REMARKS

Claims 1-11 are pending. The Applicants respectfully request the Examiner to reconsider the rejections in view of the amendments presented herewith and the following remarks.

The Applicants respectfully begin by highlighting to the Examiner the amendments now presented to claims 6-8, which addresses the preliminary issues raised with regard to the claims. The Examiner is accordingly respectfully requested to withdraw the rejections as to indefiniteness under Title 35 USC §112, paragraph 2 and statutory subject matter under §101.

Rejections under 35 USC §102(b)

The original claims were rejected by the Examiner as being anticipated by Seemann *et al.*, and by Croxtall *et al.*

A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102, however, requires a finding that each and every limitation is found in a single prior art reference. Celcritas Techs. Inc. v. Rockwell Int'l Corp., 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998). Accordingly, the Applicants respectfully remind the Examiner that any of the claims presented herewith, in order to be legally anticipated, must encompass an embodiment within the disclosure of Seemann *et al.*, -or- Croxtall *et al.*

The Applicants moreover respectfully highlight to the Examiner that the teaching in the art at the time of the Applicants' invention was that the biological activity of LC-1 was crucially dependent upon amino acids 13-25, more specifically 18 to 25 of the LC-1 peptide, not amino acids 1-12. This is in direct contrast to the present invention, which is based on the finding that amino acids 2-6 (AMVSE) of LC-1 are active *pharmacologically*, particularly in the treatment of inflammation.

The Applicants respectfully submit that there is no explicit or implicit disclosure in either of the cited documents of a medical use of a peptide falling within the scope of claim 1, or any of the claims now pending. Claim 1 has now been limited to a compound comprising a specific amino acid sequence for use as a pharmaceutical. Claims 2-3 and 5 depend from claim 1. Claim

4 is drawn toward a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients. Claim 6 is limited to a method of manufacturing a pharmaceutical composition.

Croxtall *et al.*, in sharp contrast, relates to the inhibition of the growth of A549 cells. Particularly, Croxtall reports that peptides[1] outside the scope of the claims of the present application, inhibit A549 cell growth and also suppress the release of PGE_2. PGE_2, released by A549 cells, stimulates growth of these cells. However, Croxtall specifically states that the LC-1 peptide 1-12 has no effect on the growth of A549 cells (see Croxtall *et al.*, page 154, Results Section, second sentence). Moreover, the LC-1 peptide 1-12 does not suppress the release of PGE_2 (see Croxtall *et al.*, page 155, left-hand column, final three lines).

In one assay described in Croxtall *et al.*, the LC-1 peptide 1-12 was found to inhibit growth of A549 cells, which are stimulated by the growth factor EGF. Correspondingly, the EGF-induced increase in PGE_2 was also blocked in this assay. However, the results are not an indication of a pharmacological compound of a medical utility to one skilled in the art for the LC-1 peptide 1-12. In particular there is no indication of anti-inflammatory activity as an *in vitro* therapeutic compound. Nowhere in Croxtall *et al.* is there a disclosure of a medical use for the LC-1 peptide 1-12.

The Croxtall disclosure, as a whole, teaches away from the 1-12 peptide, and that in contrast, indeed it is the LC-1 peptide 13-25 that is valuable for the inhibition of A549 cell growth. Croxtall shows comparatively that the LC-1 peptide, namely 1-12, is inactive in most assays. Accordingly, the reader is indeed led away from believing that the result in the assay with EGF stimulation even remotely suggests the LC-1 peptide 1-12 has a therapeutic use.

Furthermore, subsequent reports of the LC-1 peptide 1-12 by the same research group have failed to confirm that this peptide inhibits PGE_2 release in response to EGF. Enclosed is a copy of another article, published in March 1998, by the same research group (Croxtall *et al.*, *British Journal of Pharmacology,* 1998, 123, 975-983), which demonstrates that $LC\text{-}1_{1\text{-}12}$ is, in fact, inactive in an EGF-stimulated assay of the A549 cell line. In particular, the Examiner is respectfully referred to page 976, first column, *"Use of EGF"*. This explains that EGF

stimulates cell growth by its ability to release eicosanoids (a class of arachidonic acid derivatives, of which PGE_2 is a member). This section further explains that EGF stimulates the release of eicosanoids by activation of $cPLA_2$ (phospholipase A_2). Thus, suppression of $cPLA_2$ activation is directly related to suppression of PGE_2 release.

On page 980, first column, "*Effect of peptides on $cPLA_2$ activity*", it is stated that LC-1_{1-12} does not block activation of $cPLA_2$ in an assay involving the treatment of A549 cells with EGF. By contrast LC-1_{13-25} and dexamethasone both inhibited activiation of $cPLA_2$. The corollary is that LC-1_{1-12} will not block release of eicosanoids (including PGE_2) when A549 cells are stimulated with EGF. This is clearly contrary to the findings in Croxtall *et al.*, and fortifies the Applicant's belief that the report by Croxtall that LC-1 peptide 1-12 was found to inhibit EGF-stimulated A549 cells is erroneous.

The Applicants respectfully submit that Seemann *et al.* similarly points to the importance of amino acids 13 to 26 of Annexin 1 (formerly Lipocortin 1) and away from any function or importance to N-terminal amino acids 1 to 12. Specifically, Seemann *et al.* state in the Abstract, for example, on page 1359 that:

> "*Interestingly, a truncation of the N-terminal 26, but not the N-terminal 13 residues of annexin 1 altered its intracellular distribution, shifting it from fractions containing early to those containing late and multivesicular endosomes.*"

Seemann *et al.*, in contrast to the subject matter of the claims presented herewith, contains no disclosure or suggestion of a pharmaceutical use or medical indication for the compounds now claimed. The Examiner refers to the immunization of mice with annexin 1 from bovine lung at page 1362, column 2, second section. However, this passage relates entirely to the preparation of monoclonal antibodies and neither teaches nor suggests any pharmaceutical or therapeutic use or benefit to the mouse.

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[1] Lipocortin-1, positions 13-25 and 21-33.

Thus, the overriding perception in the art was that the biological activity of LC-1 was crucially dependent upon amino acids 13-25, more specifically 18 to 25 of the LC-1 peptide, not amino acids 1-12. This is in direct contrast to the present invention, which is based on the finding that amino acids 2 to 6 (AMVSE) of LC-1 are pharmaceutically useful, particularly in the treatment of inflammation.

The Examiner is accordingly respectfully requested to withdraw the rejections under 35 USC §102(b).

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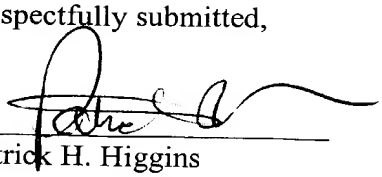
For all the foregoing reasons, the Applicants submit that Claims 1-11 are in condition for allowance. Early action toward this end is courteously solicited. *The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution.*

The Commissioner is authorized to charge any deficiency or credit any overpayment in connection herewith to Deposit Account No. 13-2165.

Respectfully submitted,



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